

# Exhaled nitric oxide and blood eosinophilia: Independent markers of preventable risk

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It is becoming increasingly clear that assessment of eosinophilic airway inflammation is moving from a “nice to do” to a “must do” for clinicians looking after patients with airways disease, particularly those with more severe and complex disease.<sup>1</sup> The benefits of corticosteroid therapy are confined to patients with this pattern of airway inflammation, and management that is fine tuned to achieve control of eosinophilic airway inflammation results in a marked reduction in the risk of severe asthma-induced<sup>2,3</sup> and chronic obstructive pulmonary disease-induced<sup>4</sup> lung attacks. Most now would be uncomfortable recommending high-intensity corticosteroid therapy (ie, regular oral prednisolone) or oral corticosteroid-sparing treatments without the additional security of demonstrating a corticosteroid-responsive pathology. In time, we suspect this will become the case for initiation of what is usually intended to be lifelong treatment with inhaled corticosteroids and for the use of systemic corticosteroids to treat acute attacks. Assessment of eosinophilic airway inflammation will be essential for the proper use of existing and potentially new biological treatment options that target the T<sub>H</sub>2 pathways leading to eosinophilic airway inflammation because efficacy is only apparent in patients with evidence of activation of that pathway.<sup>5-8</sup>

How then is the clinician to do this? Traditional measures used in asthmatic patients, including symptom scores, tests of variable airflow obstruction, and assessment of airway hyperresponsiveness, are at best weakly associated,<sup>9,10</sup> and airways disease categories, to which we remain very attached, provide a limited perspective on pathology.<sup>1,11</sup> Thus if the clinician needs to know whether eosinophilic airway inflammation is present, he or she needs to measure it. The induced sputum differential inflammatory cell count, which is regarded by many as the gold standard noninvasive method to do this, is not feasible outside a specialist setting, is not always successful, and does not provide an immediate result. We are left with less direct measures, including measurement of fraction of exhaled nitric oxide (FENO) values, peripheral blood eosinophil counts, and periostin levels.

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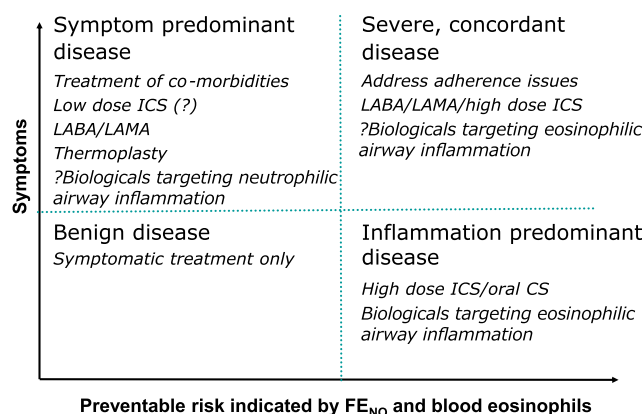
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In this issue of the *Journal*, we have new information on the relationship between the first 2 measures and asthma diagnosis and risk of asthma attacks. Malinovschi et al<sup>12</sup> used data from 12,408 participants in the National Health and Nutrition Examination Survey 2007-2008 and 2009-2010 to investigate the relationship between FENO values and blood eosinophil counts and current wheeze, asthma diagnosis, asthma attacks, and asthma-related emergency department visits within the last 12 months. Asthma symptoms, diagnosis, and events were assessed by means of questionnaire. The prevalence of wheeze, asthma, and asthma attacks increased independently and additively with increasing FENO values and blood eosinophil counts, whereas the prevalence of asthma-related emergency department visits was associated with increased blood eosinophil counts. Compared with subjects with normal values, the adjusted odds ratios of having wheeze, asthma, asthma attacks, and asthma-related emergency department visits in patients with both a FENO value of 50 ppb or greater and a blood eosinophil count of  $0.5 \times 10^9/L$  or greater were 4.5, 5.1, 5.4, and 2.9, respectively.

Two aspects of the study strike us as important. First, the association between these biomarkers and the risk of asthma symptoms and attacks was independent of current treatment and was as great or greater than that of other risk factors, such as obesity, female sex, smoking, and rhinitis. However, unlike these and other more well-recognized markers of risk, an increased FENO value and blood eosinophilia indicate activation of a pathway that can be suppressed relatively easily with both existing and new treatments. Randomized controlled trials have shown that sputum eosinophilia,<sup>2,3,13</sup> blood eosinophilia,<sup>5</sup> and an increased FENO value<sup>8,14</sup> are associated with a markedly increased risk of asthma attacks and that this association is independent of symptom control. This risk can be reduced by targeted corticosteroids<sup>2,3,14</sup> or more specific inhibitors of T<sub>H</sub>2 pathways<sup>5,7,8,13</sup> without much effect on symptoms or lung function. Thus both FENO values and blood eosinophilia are biomarkers of preventable risk mediated by persistent eosinophilic airway inflammation, and it cannot be assumed that symptom control equals inflammation control. The clear implication is that for optimum control of inflammatory airway diseases, we need to move on from a strategy that seeks to suppress symptoms and normalize lung function to one that includes the extra goal of minimizing preventable risk, as indicated by blood eosinophilia, an increased FENO value, or both (Fig 1).

The second noteworthy aspect of the study of Malinovschi et al<sup>12</sup> is that FENO values and blood eosinophil counts were not clearly related, suggesting that they might identify different aspects of T<sub>H</sub>2-mediated inflammation. Might this difference be clinically important? The authors' suggestion that blood eosinophilia is a marker of more severe systemic inflammation is entirely plausible because it implies a strong chemokine signal



**FIG 1.** The future management of inflammatory airway disease with the focus on managing day-day symptoms, optimizing lung function, and reducing preventable risk, as indicated by blood eosinophilia, an increased FENO value, or both. CS, Corticosteroid; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting antimuscarinic agent.

from the airways and more extensive eosinophilic airway inflammation, perhaps involving the small airways. Therefore it might be associated with relative inhaled corticosteroid resistance and a greater requirement for systemic therapy. Inhaled corticosteroid-unresponsive but oral corticosteroid-responsive eosinophilic airway inflammation is particularly well recognized in patients with eosinophilic chronic obstructive pulmonary disease,<sup>15</sup> a condition in which the blood eosinophil count has emerged as a robust marker of eosinophilic airway inflammation<sup>16</sup> and oral corticosteroid responsiveness.<sup>17</sup> It might also be a feature of asthma-induced and chronic obstructive pulmonary disease-induced lung attacks, in which a requirement for oral corticosteroids is also well recognized. The authors speculate that patients with blood eosinophilia have greater involvement of IL-5, the main cytokine involved in eosinophil production and mobilization into the systemic circulation and airway. In keeping with this, a recent large randomized controlled trial<sup>5</sup> showed that the blood eosinophil count was the biomarker most closely related to a positive response to mepolizumab (anti-IL-5).

In contrast, an increased FENO value indicates local IL-4- and IL-13-mediated mechanisms in the bronchial mucosa and might therefore be more closely associated with inhaled corticosteroid-responsive disease and a response to IL-4 blockade, IL-13 blockade, or both and less closely associated with the response to IL-5 blockade and the more systemic disease seen in patients with sudden severe attacks. The findings of Malinovschi et al<sup>12</sup> provide some support for the latter because although an isolated increased FENO value was associated with the risk of attacks, it was not associated with the risk of sudden episodes resulting in emergency department visits. It might be that blood eosinophilia, but not an increased FENO value, identifies patients who are at risk of sudden-onset attacks, perhaps because it indicates a large potential systemic response to increased chemokine and adhesion molecule expression in the airway. Epidemiologic evidence of a strong association between blood eosinophilia and the risk of fatal attacks of obstructive airway disease<sup>18</sup> supports this view. Clinical trial data are also entirely in keeping with the assumption that FENO values reflect IL-4- and IL-13-mediated airway responses because an increased FENO value is an excellent marker

of a clinical response to inhaled corticosteroids,<sup>19</sup> lebrikizumab (anti-IL-13),<sup>6</sup> and omalizumab<sup>8</sup> but not mepolizumab.<sup>5</sup>

The implication of the findings of Malinovschi et al<sup>12</sup> is that we should view FENO values and blood eosinophil counts as complementary biomarkers of a clinically important pattern of airway inflammation. Potentially, each might associate differently with important clinical events and treatment responses. The future might be to use these and other biomarkers to define clinically important subphenotypes of eosinophilic airway disease and refine our risk-reduction strategy accordingly.

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